

# Preserving the Miracle of Antibiotics:

## The Antimicrobial Stewardship Program

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### Objectives

1. To depict the current antimicrobial crisis
2. To describe Antimicrobial Stewardship Program
3. To acknowledge main diseases treated inappropriately
4. To introduce new ASP initiatives

“the public will demand [the drug and] then will begin an era of abuses. The microbes are educated to resist penicillin and a host of penicillin-fast organisms is bred out which can be passed to other individuals and perhaps from there to others until they reach someone who gets a septicemia or a pneumonia which penicillin cannot save.

In such a case the thoughtless person playing with penicillin treatment is morally responsible for the death of the man who finally succumbs to infection with the penicillin-resistant organism. I hope the evil can be averted.”

*Fleming A. New York Times 1945*



► **Miracle of antibiotics now endangered**

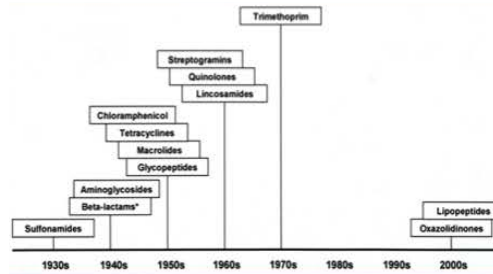
- owing to rapid escalation of antibiotic (Abx) resistance

**COMBINED WITH**

- equally rapid ↓ in discovery/development of new Abx

## Sobering Facts

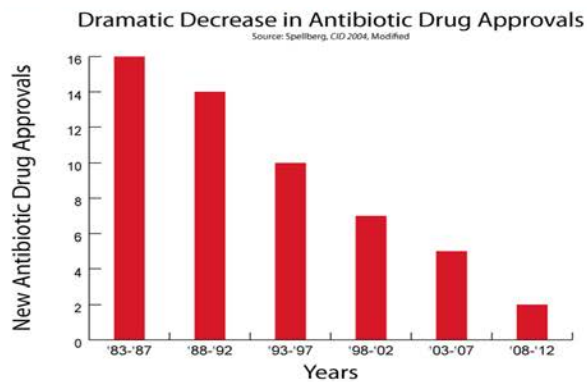
- ▶ 15/18 large pharm companies totally left the antibiotic field
- ▶ Only 2 drugs with new targets (linezolid and daptomycin) have been introduced in the past 15 years



Infectious Diseases Society of America. Clin Infect Dis 2010

## Sobering Facts

No new class of Abx for Gram (-) bacilli in 4 decades



Infectious Diseases Society of America. Clin Infect Dis 2010

## Sobering Facts

### United States

**4.6%** of global population  
**46%** of the global Abx market!!!

In 2009: **>3 million kg** of Abx administered to humans in US!!

**13 million kg** administered to animals for growth promotion!!!!

US Food and Drug Administration, 2011  
 Marshall BM et al. Clin Microbiol Rev 2011



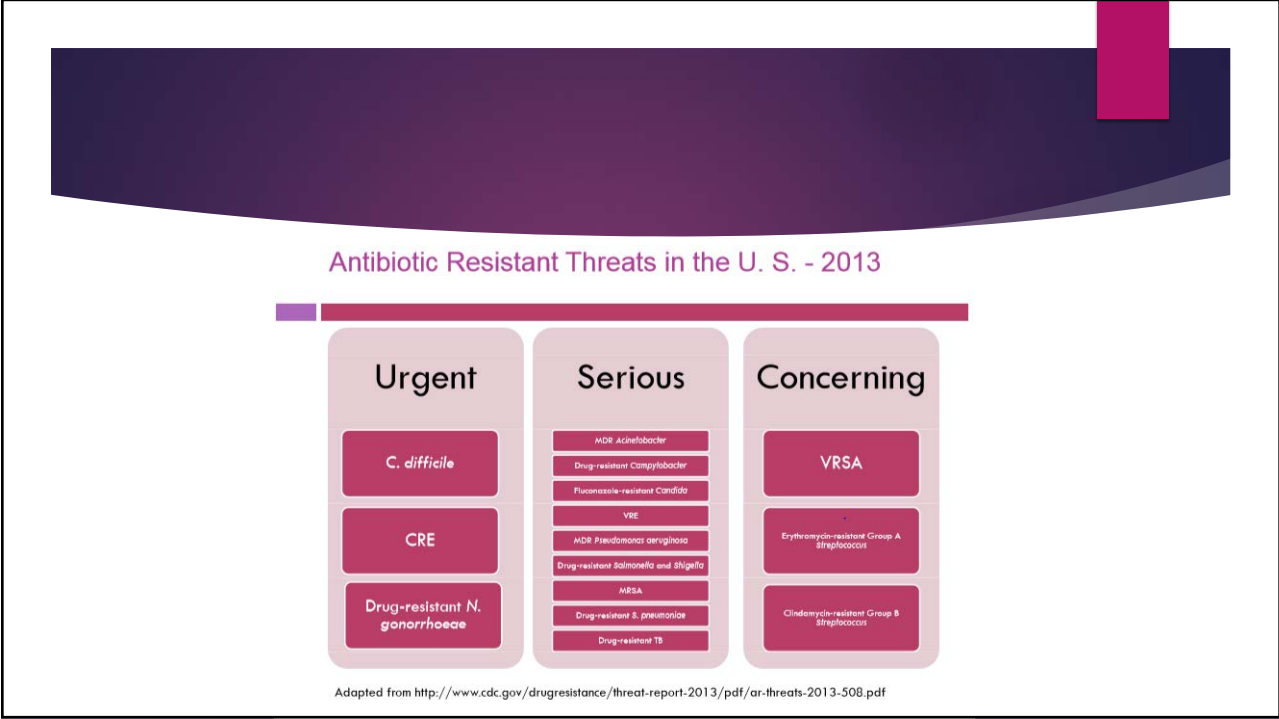
## Consequences to Human Health..... no clear benefit to farmers

- ▶ **Direct effect noted > 35 yrs ago:**  
 ↑↑ rates of Abx resistance in intestinal flora of animals/farmers
- ▶ **Molecular typing:** resistant bacteria in farm animals DO reach consumers in meat products

### Impact on Environmental Microbiome

- ▶ 90% of Abx given to animals excreted in urine/stool and then widely dispersed → fertilizer, surface runoff, groundwater

Ansari F et al. J Antimicrob Chemother 2010  
 Wright GD. Curr Opin Microbiol 2010




## Since 2000...

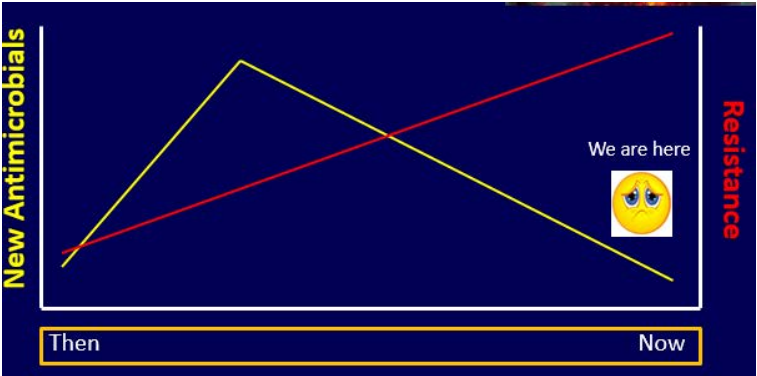
<b>E</b>	<i>nterococcus</i>
<b>S</b>	<i>taphylococcus</i>
<b>K</b>	<i>lebsiella (KPC)</i>
<b>A</b>	<i>cinetobacter</i>
<b>P</b>	<i>seudomonas</i>
<b>E</b>	SBL

- ▶ Most important causes of Abx resistance crisis
- ▶ MRSA kills more Americans every year (~19,000) than COPD, HIV, Parkinson's, homicide combined
- ▶ Cost to healthcare system of resistant infections:
  - \$21 – \$34 billion/yr**
  - > 8 million additional hospital days/yr**

# Antibiotic Apocalypse



Bartlett JG. Medscape



# Return to Pre-Antibiotic Era???

- ▶ Fundamental impact of introduction of Abx was dramatic decline in death from bacterial infections of all types

Disease	Pre-Antibiotic Mortality Rate	Antibiotic Mortality Rate	Change in Mortality
Community Pneumonia [53]	~ 23%	~ 7%	-16%
Nosocomial Pneumonia [54]	~ 60%	~ 30%	-30%
Bacterial Endocarditis [112-115]	~ 100%	~ 25%	-75%
Bacterial Meningitis [116-117]	>80%	<20%	-60%
Skin Infection [55, 118]	~ 11%	<.5%	-10%
By comparison, treatment of myocardial infarction (i.e., heart attack) with aspirin or streptokinase [119]			-3%

*Infectious Diseases Society of America. Policy Paper. Clin Infect Dis 2011*

## 7 Ways to Preserve the Miracle of Antibiotics

1. Restrict use of Abx in agriculture
2. Restrict FDA Abx barriers
3. Facilitate public-private partnerships for Abx development
4. Prevent selected nosocomial infections using an established systematic implementation plan
5. Establish transparent public reporting of data on Abx use across medical centers AND individual providers to enable national benchmarking and reimbursement modification
6. Promote new diagnostics: point-of-care molecular methods
7. Aggressively promote Antibiotic Stewardship

*Bartlett JG et al. Clin Infect Dis 2013*

## What is Antimicrobial Stewardship

- ▶ Multifaceted approach aimed at achieving goals:
  - combating emergence of resistance
  - improving patient outcomes
  - controlling healthcare cost

By improving/optimizing antimicrobial utilization



*Lawrence KL et al. Am J Respir Crit Care Med 2009*

## Antimicrobial Stewardship Goals

### Primary Goal

To assist care providers to optimize clinical outcomes while minimizing unintended consequences of antimicrobial use

**(toxicity, emergence of resistance, selection of pathogenic organisms)**

Appropriate use of antimicrobials:

- essential component of patient safety
- deserves careful oversight and guidance

*Dellit TH et al. Clin Infect Dis 2007*

## Antimicrobial Stewardship Program

- ▶ Numerous studies demonstrate that **50%** of antimicrobial use is inappropriate  
**(↑ed LOS, ADE, costs)**
- ▶ Inappropriate/unnecessary use → increased selection of resistant pathogens

*John JF. Clin Infect Dis 1997*

*Roberts AW. Am J Hosp Pharm 1972*

*Reimann HA. Med Clin North Am 1961*    *McGowan JE Jr. Emerg Infect Dis 2001*

*Kislak JW. N Engl J Med 1964*

*Cosgrove SE. Clin Infect Dis 2003*



# Antimicrobial Stewardship Team

**Core Members**

- 1) ID attending physician
- 2) ID clinical pharmacist(s)
- 3) Information System specialist



- Optimally, team includes:
  - clinical microbiologist to provide surveillance data on antimicrobial resistance
  - infection control professional to coordinate efforts on improving antimicrobial usage

# Elements of Effective ASP

**CORE ACTIVE STRATEGIES**

Prospective audit with intervention and feedback

Preauthorization requirements for specific agents

**SUPPLEMENTAL STRATEGIES**

- |                              |                            |
|------------------------------|----------------------------|
| Education                    | Streamlining/de-escalation |
| Guidelines/clinical pathways | Dose optimization          |
| Antimicrobial order forms    | Conversion from IV to PO   |

## Preauthorization Requirements: Specific Agents

- ▶ Antimicrobial restriction through requirement of preauthorization and justification
  - most effective method of achieving goal of controlling use
- ▶ Longitudinal studies implementing restrictive policies consistently demonstrate:
  - significant ↓ in initial use of targeted agents
  - ↓ in antimicrobial use: **(22%-36%)**
  - annual antimicrobial cost savings: **\$300,000-\$900,000**

*Seligman SJ. Am J Med 1981*

*Woodward RS. Am J Med 1987*

- Linezolid
- Daptomycin
- Ceftaroline
- Tigecycline
- Ertapenem
- Meropenem
- Amikacin
- Streptomycin
- Aztreonam
- Colistin
- Fosfomycin
- Voriconazole
- Micafungin
- Amphotericin B
- Non-formulary antimicrobials

\* Requires ID consultation if continued

## Prospective Audit

### Effective audit with intervention and feedback

- facilitated through computer surveillance of antimicrobial use
- allows for targeting specific services/units where issues exist
- allows for identification of patients receiving particular agents or combinations of agents that may benefit from intervention
- each intervention provides opportunity for provider education

- Ciprofloxacin
- Levofloxacin
- Ceftriaxone
- Cefepime
- Piperacillin/tazobactam
- Clindamycin
- Oral vancomycin

## Guidelines and Clinical Pathways

- ▶ Clinical practice guidelines produced with ↑ing frequency
  - Goal:** ensure high quality, evidence-based care
- ▶ Physicians usually agree with national guidelines
  - absence of accompanying strategies for local implementation    presents formidable barrier
- ▶ ASP facilitates multidisciplinary development of evidence-based practice guidelines
  - incorporating local microbiology and resistance patterns

## De-escalation of Therapy

- ▶ When microbiologic data becomes available, streamlining or de-escalation to more targeted therapy:
  - ↓es antimicrobial **exposure**
  - limits development of **resistance**
  - contains **costs**

*Briceland LL. Arch Intern Med 1988*



**"Do not use a cannon to kill a mosquito"**  
- Confucius (551–479 BC)

**LIMIT COLLATERAL DAMAGE**

## IV to PO Conversion

- ▶ Therapy for hospitalized patients with serious infections:
  - generally initiated with IV therapy
- ▶ Enhanced **oral bioavailability** of certain agents allows PO conversion once patient meets defined clinical criteria
- ▶ Results in ↓'ed LOS, potential complications due to IV access, and health care costs

## Skin and Soft Tissue Infections : Key Points

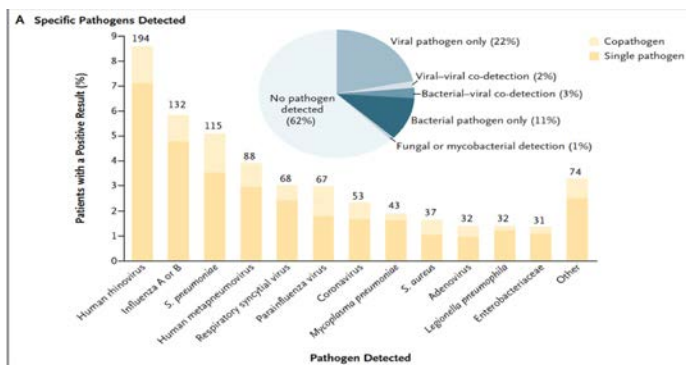
- ▶ In cases of uncomplicated SSTIs, only need to treat beta-hemolytic streptococci
  - ▶ No need for extended anaerobic or extended GNR coverage
  - ▶ Cefazolin is recommended IV drug of choice (Keflex as stepdown option)
  
- ▶ In cases of uncomplicated SSTIs with purulence, empiric therapy for MRSA should be given in addition to therapy against beta-hemolytic streptococci
  - ▶ Vancomycin is recommended IV drug of choice
  - ▶ Step down options include clindamycin monotherapy OR either TMP/SMX or doxycycline in combination with Keflex
  - ▶ TMP/SMX and doxycycline do not have reliable activity against beta-hemolytic streptococci

- ▶ Duration of therapy for uncomplicated SSTIs should be 5-7d total
  - ▶ Due to paucibacillary nature of disease, organisms eradicated within 5 days of therapy
  - ▶ May take more time for erythema and swelling associated with excessive inflammation to resolve
  - ▶ Not necessary to extend therapy until resolution of signs of residual inflammation
  
- ▶ Use of anti-inflammatory agents has been shown to greatly accelerate resolution of cellulitis
  - ▶ Ibuprofen 600mg TID for 5d or prednisone 40mg daily

# Community Acquired Pneumonia

- Classification
  - bye bye HCAP
- Microbiology
  - **Incidence of viral etiology**
  - Relevance of Resistance
- **Diagnostic Studies**
  - **Molecular**
  - **Procalcitonin**
- **Stewardship**
  - **Pathogen-direction therapy**
  - **De-escalation**
  - **Duration**
- Therapy
  - FQ vs Combination
    - Sequence of combination
  - 'Atypical' coverage
  - MRSA
  - Adjunctive care:
    - Steroids
  - Prevention (better vaccines)

## Pathogen Detection among Hospitalized Adults with CAP Enrolled in EPIC Study – Jan 1, 2010–June 30, 2012



Jain S. Self WH, **Wunderink RG** et al. NEJM 2015

## IDSA and ATS Guidelines

“For patients with HAP/VAP, we suggest using PCT levels plus clinical criteria to guide the discontinuation of antibiotic therapy, rather than clinical criteria alone”

Kalil AC et al. Clin Infect Dis 2016

PCT < 0.1 ug/ml	Bacterial infection VERY UNLIKELY	NO ANTIMICROBIALS	Consider repeat 6-24hrs based on clinical status
PCT 0.1-0.25 ug/ml	Bacterial infection UNLIKELY	NO ANTIMICROBIALS	Use of ABX based on clinical status ('unstable') & judgment
PCT > 0.25-0.5 ug/ml	Bacterial infection LIKELY	YES ANTIMICROBIALS	Repeat PCT day 3, 5, 7 (for Duration)
PCT > 0.5 ug/ml	Bacterial infection VERY LIKELY	YES ANTIMICROBIALS	CONSIDER STOP ABX when 80=90% decrease; if PCT remains high consider treatment failure

File TM Jr. Clin Chest Med. 2011; modified from Schuetz P. et al. Eur Respir J 2011;37(2): 384-92.



## Length of therapy


- Adult Pts ( $\geq 18$  yrs) in Netherlands; PSI of  $\leq 110$
- All treated with IV Amoxicillin and assessed at 72 hours for response
  - ▶ If good clinical response and able to take oral therapy, randomized to 5 more days of oral amoxicillin 750 mg TID (n=63) or placebo (n=56)
  - ▶ RESULT: 3 days as effective

El Moussaouri et al. BMJ 2006; 332: 1355


## Urinary tract infections

- ▶ UTI's are the most common bacterial infection encountered in ambulatory care settings in the United States, accounting for 8.6 million visits in 2017.
- ▶ Catheter-associated UTIs are the most common type of healthcare-associated infection reported to the National Healthcare Safety Network (NHSN) and the most commonly treated infections in residents of long-term care facilities.
- ▶ 10.8 million patients in the United States visited an Emergency Department for the treatment of a UTI between 2006 and 2009.
- ▶ The economic burden of utilizing the ED for the treatment of UTIs is estimated to be \$2 billion US dollars annually.

Antimicrobial Stewardship and Urinary Tract Infections Lilian M. Abbo \* and Thomas M. Hooton Department of Medicine, Division of Infectious Diseases, University of Miami Miller School of Medicine, 1120 NW 14th Street, Suite 851, Miami, FL 33136, USA

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- ▶ The diagnosis of UTI is primarily based on signs and symptoms rather than isolated laboratory findings.
  - ▶ Urine cultures are often not useful for acute uncomplicated cystitis, are recommended for patients with uncomplicated pyelonephritis and complicated UTI, and with few exceptions, should not be collected in asymptomatic patients.
  - ▶ Antimicrobial therapy should be tailored to each patient taking into consideration the severity of disease, individual and local patterns of antimicrobial resistance and the potential for collateral damage associated with antimicrobial use.

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- ▶ Selecting the correct drug, dose, and shortest clinically effective duration of therapy when possible, is key to optimal antimicrobial stewardship.
  - ▶ Strategies to prevent recurrent UTIs and catheter-associated bacteriuria could greatly reduce the use of antimicrobials and are therefore key stewardship modalities. It is the responsibility of all healthcare providers to practice antimicrobial stewardship and prescribe antimicrobials prudently, thoughtfully and rationally

**Table 1.** Opportunities for antimicrobial stewardship and urinary tract infections.

<p>Use antimicrobials only when appropriate</p> <ul style="list-style-type: none"> <li>ASB should be screened for and treated only in select conditions, such as pregnancy and prior to urologic surgery</li> </ul> <p>Use the appropriate antimicrobial</p> <ul style="list-style-type: none"> <li>Empiric choice—for cystitis, use an agent with low risk of collateral damage</li> <li>For uncomplicated pyelonephritis and complicated UTIs, obtain pre-treatment urine culture and de-escalate as appropriate to narrow spectrum agent</li> </ul> <p>Treat for appropriate duration</p> <ul style="list-style-type: none"> <li>Use short-course treatment for cystitis</li> <li>Short-course regimens are appropriate for some patients with complicated UTI</li> </ul> <p>Consider non-antimicrobial preventive strategies for recurrent uncomplicated cystitis *</p> <ul style="list-style-type: none"> <li>Behavioral modification</li> <li>D-mannose</li> <li>Cranberry</li> <li>Topical estrogens in postmenopausal women</li> <li>Probiotics</li> <li>Oral immunostimulants</li> <li>Antimicrobials as a last resort</li> </ul>
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\* Most non-antimicrobial preventive strategies have either not been studied in prospective trials or have not been shown to be effective in trials to date, but are reasonable to try or continue if the patient so chooses and if they are considered to be safe.

## Duration of Therapy

### Right drug, right dose, right route, right duration

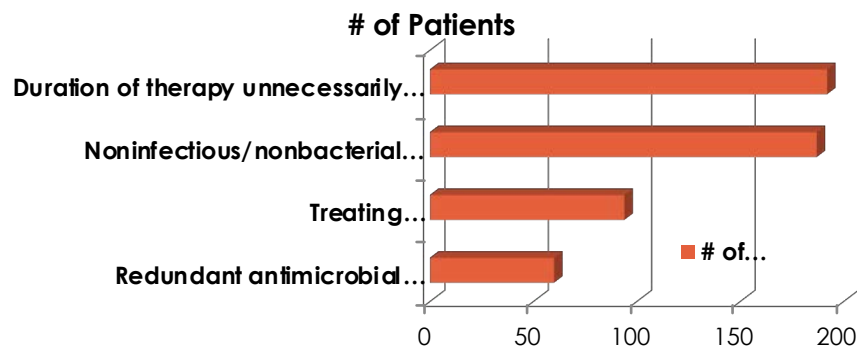
- ▶ Optimize safety – most effective and least toxic agent
  - ▶ Optimize duration right duration to maximize clinical cure & minimize exposure thus reducing ADEs and CDI
- ▶ Reduce resistance – most narrow spectrum agent at best dose to minimize selection of resistance
  - ▶ The shortest duration needed to cure reduces selection of resistance
- ▶ Decrease costs – most cost-effective agent provide the most efficient cure
  - ▶ Optimizing duration can save money for patient/hospital

Barlam TF. Duration of Therapy: Our Role as Stewards. IDWeek 2015

## Duration of Therapy

- ▶ **Community acquired pneumonia:**
  - ▶ 5 days recommended
  - ▶ 10-14 routinely prescribed
  
- ▶ **Acute bacterial skin and skin structure infections:**
  - ▶ 5-7 days recommended
  - ▶ 14 days routinely prescribed
  
- ▶ **Pyelonephritis:**
  - ▶ If susceptible, 7 days or ciprofloxacin or 5 days of levofloxacin recommended
  - ▶ At least 14 days routinely prescribed

## Reasons for Unnecessary Days of Therapy for All Antimicrobials



Hecker MT et al. Arch Intern Med 2003;163:972-978

## Potential Roadblocks

- ▶ Clinicians resist change in practice
  - ▶ Disrupts their long held beliefs
- ▶ Limited high-quality data on duration of therapy with few RCTs for most disease states
- ▶ Duration recommendations absent or vague in many treatment guidelines
  - ▶ Many based upon expert opinion rather than RCTs
- ▶ Many treat longer "just to be safe"


*Barlam TF. Duration of Therapy: Our Role as Stewards. IDWeek 2015  
Rice LB Clin Infect Dis 2008;46:401-8*

## Millcreek Community Hospital

- ▶ Team:
  1. Clinical pharmacist at MCH
  2. Clinical pharmacist at LNR and SLC
  3. ID specialist
- ▶ Twice a week meetings and discussion about any patient on abx
- ▶ Goals:
  - ▶ Outpatient and ER interventions
  - ▶ Education
  - ▶ Protocols
  - ▶ Prospective audit with intervention and feedback
  - ▶ Preauthorization requirements for specific agents



# Questions ?



# Thank you